REMARKS

The specification has been amended as set forth above. Specifically, the specification has been amended to include SEQ ID NOs. and to correct several typographical errors.

Claims 13-17 were previously withdrawn from consideration due to the restriction requirement. Applicants now cancel Claims 13-17 without prejudice and reserve the right to pursue those claims in future prosecution. Also, Claims 4 and 21 have been cancelled without prejudice. New Claims 23-44 have been added as set forth above. Thus, Claims 1-3, 5-6, 18-20 and 22-44 are presented for examination. The new claims are supported throughout the specification and by the claims as filed. Therefore, no new matter has been added.

Claims 1 and 22 and have been amended as shown above. Support for the amendments to the claims is found, for example, in the claims as filed and in the specification at pages 1-5 and 21-22. Therefore, no new matter has been added. Amendments to the claims are shown above with deletions shown with ~~strike-through text~~ and additions shown with underlined text.

Sequence Compliance

As requested in the Office Action, Applicants have amended the specification to comply with the sequence rules by inserting SEQ ID NOs. next to the corresponding sequences in the specification at pages 6-8 and 24-25.

Discussion of Objection under 35 U.S.C. § 132

In the Office Action the Examiner objected to the previous amendment because allegedly it introduced new matter. In particular the Examiner argued that there is no support for the recitation of "60% identical to the sequences selected from the group consisting of SEQ ID NO:2 and 4" in Claim 22 and "more than 80% identical to ..." in Claim 23. The Examiner acknowledged that the specification provides support for 50%, 70%, 90% and 99%.

Respectfully, Applicants draw the Examiner's attention to the specification at page 23 where homology is defined as "identity in sequence of at least 40%, in particular of at least 60%, preferably of more than 80% and more preferably of more than 90%." In view of this, Applicants submit that no new matter has been added by the prior amendments to Claims 22 and 23. Nonetheless, Applicants have amended Claims 22 and 23, as set forth above. Claim 22

has been amended to recite "the protein having an amino acid sequence which is at least 70% identical ..." Claim 23 has been amended to recite that the protein "has an amino acid sequence which is at least 80% identical ..." Both amendments are fully supported by the specification.

In view of the above comments, Applicants respectfully request withdrawal of the objection under § 132.

Discussion of rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-3 and 22-23 were rejected under 35 U.S.C. § 112, first paragraph as not being enabled. The Office Action asserts that the specification, while being enabling for the process of producing a number of specified exemplary glycolipids, does not reasonably provide enablement for a process of producing any or all types of glycolipids. The Office Action therefore argues that undue experimentation would be required to make any or all types of glycolipids.

Also, the Office Action asserts that Claims 1-6 and 18-23, while being enabled for a process of making glycolipids using a processive diacylglycerol glycosyltransferase (PDG) enzyme with the sequence of SEQ ID NOs: 2 or 4, does not reasonably provide enablement for such a process using any PDG enzyme from any and all sources.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). *In re Wands* summarized the factors that are to be considered in determining whether a disclosure would require undue experimentation. 858 F.2d 731, 737 (Fed. Cir. 1988) (summarizing *In re Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). The factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of unpredictability of the art, and (8) the breadth of the claims.

Rejection of Claims 1-3 and 22-23

The Office Action rejected Claims 1-3 and 22-23 as not being enabled alleging that the specification, while being enabling for the process of producing a number of specified exemplary

glycolipids, does not reasonably provide enablement for a process of producing any or all types of glycolipids.

Claims 1 and 22 have been amended as set forth above to specifically list the particular glycolipids produced by the claimed processes. Specifically, Claims 1 and 22 recite processes for the production of glycosyl diacylglycerols, sterolglycosides, glycocerebrosides, alkyl-β-D-glycopyranosides, and phosphoglycolipids. The making and using of each of these is disclosed in the specification and claims as filed. Therefore, Applicants assert that these claims are fully enabled, and respectfully request withdrawal of the rejection under § 112, first paragraph.

Rejection of Claims 1-6 and 18-23

The Office Action also rejected Claims 1-6 and 18-23 as not being enabled alleging that the specification, while being enabling for processes of making glycolipids using a processive diacylglycerol glycosyltransferase (PDG) enzyme with SEQ ID NOs: 2 or 4, does not reasonably provide enablement for such processes using any PDG enzyme from any and all sources.

Respectfully, Applicants disagree with the instant rejection for the reasons set forth below. With regard to Claims 1-6, Applicants assert that the claims are enabled because the skilled artisan can easily make and use any PDG enzyme without undue experimentation. The test for "undue experimentation" is "not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737 (quoting *In re Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Int. 1982). Here, the experimentation necessary, to make and use any PDG enzyme for transferring a hexose to a lipid acceptor, is merely routine and the specification provides ample guidance on how the experimentation should proceed.

The specification provides abundant guidance and direction commensurate in scope with the claims. Procedures are provided for isolating, cloning, characterizing and using nucleic acids encoding a PDG that can successively transfer a hexose molecule to a lipid acceptor, as well as guidance for obtaining the expressed PDG, characterizing it and using it. *See* specification at pages 7-23. The specification explains that standard techniques are used for DNA isolation, restriction analysis, and ligation. *See id.* at page 7 and 22-23. Source organisms and their DNA can be obtained from known sources. *See id.* at pages 7-8. Exemplary PCR primers and PCR

protocols are provided. *See id.* at page 8. The specification teaches how to express and extract the PDG, as well as number of analysis techniques, including SDS page, chromatography, mass spectrometry, and nuclear magnetic resonance imaging. *See id.* at pages 10-18. Standard enzyme assays for determining the activity of the PDGs are disclosed. *See id.* at pages 19-20. The specification provides techniques for easy characterization of the PDG activity and for analyzing substrate specificity. *See id.* at pages 20-22.

Two working examples illustrate the isolation, cloning, and expression of sequences encoding PDGs from bacteria. The person of ordinary skill the art can easily follow the guidance and direction provided in the specification, as illustrated by the working examples, and make and use PDGs that transfer hexose to a lipid acceptor without undue experimentation. All of the necessary guidance and techniques are disclosed and/or familiar to the skilled artisan.

For the first time, Applicants have disclosed and characterized glycosyl transferases involved in lipid biosynthesis that can transfer sugar molecules to two different substrates ("processive transfer"), for example, a pure lipid in the first step and a lipid-bound sugar in the second and further steps. This means that the principle of the processive glycosylation was demonstrated for the first time in the present invention, and the proof of principle is provided by describing the enzymes from *S. aureus* and *B. subtilis*. With this information, the skilled artisan can easily make and use the fully scope of the claimed invention with routine procedures.

The Office Action disputes this assertion, referencing *Saxena et al.* ("Saxena") (J. Bacteriology, 1995, Vol. 177(6):1419-1424). The Office Action alleges that Saxena disclosed processive glycosyl transferases capable of transferring a sugar molecule to a lipid. However, Saxena only disclosed processive glycosyl transferases capable of transferring sugar to growing glycan chains, but not to lipids, such as presently claimed. For example, the paragraph cited by the Examiner, the first paragraph of column one on page 1419, refers to processive enzymes for cellulose synthase or chitin synthase, which transfer multiple sugar residues to their non-lipid acceptors. Nowhere does Saxena describe glycosyl transferases that transfer to lipid acceptors.

Processive lipid glycosyl transferases are able to transfer UDP-sugar residues to a lipid acceptor or a lipid bound sugar residue. *See for example*, Figure 12 (the first sugar acceptor is a diacylglycerol, the second is a monodiacylglycerol, and the third is a tridiacylglycerol). None of the processive cellulose or chitin glycosyl transferases as described by *Saxena* are able to use

anything other than glycan chains as the sugar acceptor. Therefore, the Applicants are the first to disclose the claimed class of PDGs.

Also, submitted herewith as part of a supplemental Information Disclosure Statement is *Koyama et al.* ("*Koyama*") (PNAS 94:9091-9095 (1997)). *Koyama* described chitin synthases, hyaluron synthases and N-acetyleglucosamin transferases, which function according to the same mechanism as cellulose synthases as described by *Saxena*. These enzymes have three reaction sites (*see* Figure 4 of *Saxena*), which are only able to bind sugar residues, but no lipids. Thus, the processive reaction mechanism of the present claims is also novel in view of *Koyama*.

Further, the claims have been amended to specify particular glycolipids that are made by the PDGs. The specification describes techniques, analysis, and assays to confirm that the PDGs act to produce those specific products. Thus, the scope of the amended claims bears a reasonable correlation with the scope of enablement.

To summarize, the specification teaches those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. Any experimentation that is necessary is not undue and is certainly justified in view Applicants pioneering discovery. Applicants have provided abundant direction and guidance for making and using any PDG. Furthermore, the specification includes working examples of the novel PDGs. Applicants have disclosed examples of how to make and use the claimed invention, including DNA and amino acid sequences from two different bacteria. The person of ordinary skill can use those sequences to isolate, clone and express additional PDGs from other organisms. The skilled artisan also can analyze and confirm the character of the expressed enzymes using the assays and techniques disclosed in the specification, thus eliminating any unpredictability as to the nature of the expressed products. The scope of the claims as amended further results in enablement commensurate therewith.

For the above reasons, Applicants submit that the claims as amended are enabled commensurate with their scope and Applicants respectfully request withdrawal of the rejection under § 112, first paragraph.

Discussion of rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the claims are directed to the use of polypeptides derived from SEQ ID NOs. 2 and 4, while the specification fails to provide description of modified polypeptides encompassed by the claims.

Applicants respectfully disagree and assert that the specification provides ample teaching to describe the full scope of the claims. The written description requirement can be met in a variety of ways. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." M.P.E.P. § 2163(I); and *see, e.g.*, *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one may define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *See Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002) (citing *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971)).

As set forth in the *Written Description Guidelines*, all disclosed distinguishing identifying characteristics are to be considered, including the level of skill and knowledge in the art, partial structures, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, method of making, and any combinations thereof. *See id.* at 1106. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other characteristics may demonstrate the requisite possession. "Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." *Id.* "It

is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Particularly, the Federal Circuit recently emphasized that "functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics" is sufficient to satisfy the requirements of § 112, first paragraph. *Id.* In that case, the patent specification failed to disclose the exact sequences of the claimed genus of probes. *See id. at 1611.*

Here, the specification describes the claimed invention by sufficiently identifying characteristics to distinguish the claimed invention and to show possession at the time of filing. The specification describes several working examples of nucleic acids (SEQ ID NOs: 1 and 3) encoding PDGs as well as the amino acid sequences of exemplary PDGs (SEQ ID NOs: 2 and 4). The specification provides partial sequences for some members of the genus of PDGs. *See* specification at page 6 line 23 to page 7, line 6. For example, the proteins can have more than 5 amino acids within the amino acid sequence EHQPDIII (SEQ ID NO. 5). That sequence is identical with the amino acid sequence of the proteins from *B. subtilis* and/or *S. aureus*. Also, the proteins can preferably have more than 6 amino acids within the amino acid sequence QVVVVCGKN (SEQ ID NO. 6) or the amino acid sequence DCMITKPG (SEQ ID NO. 7), both of which are identical with the amino acid sequence of the proteins from *B. subtilis* and/or *S. aureus*. Furthermore, for example, more preferably, the encoded protein can include the amino acid sequence MITKPGGITxTE (SEQ ID NO. 8), or the amino acid sequence VKxTGIPI (SEQ ID NO. 9), or the amino acid sequence ZPDIIIxxxP (SEQ ID NO. 10), which are identical to the sequence found in *B. subtilis* and/or *S. aureus*, and where x is any amino acid and where Z represents Q or K.

In addition to working examples and partial sequences, the specification provides functional information including assays and techniques for analyzing and characterizing the activity of the PDGs. These routine assays permit the skilled artisan to distinguish members of the claimed genus. Further, the scope of the amended claims is limited to a process that uses PDGs to produce only the listed glycolipids. PDGs that produce those glycolipids are easily characterized and recognized using the disclosed assays and techniques. This combination of complete and partial structures combined with functional teachings demonstrates to the skilled

artisan that Applicants possessed the full genus of PDGs at the time of filing the application in compliance with the first paragraph of § 112.

For the reasons stated above, Applicants request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Conclusion

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the cosmetic appearance of the claims or to correct grammatical mistakes or ambiguities. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 22, 2003

By: _____

AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 20,995
(619) 235-8550

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